

Inventors: Al-Obeidi et al.
Serial No.: 09/211,715 [9543]
Filed: December 14, 1998
Page 2

0 or 1. A compound of the invention is characterized, in part, in that it exhibits a specific inhibition of factor Xa activity with a K_i of $\leq 100 \mu\text{M}$, preferably $\leq 2 \text{ nM}$, and does not substantially inhibit the activity of other proteases involved in the coagulation cascade. The invention further provides methods of specifically inhibiting the activity of factor Xa and of inhibiting blood clotting in vitro and in an individual and methods of detecting factor Xa levels or activity.

To the Claims

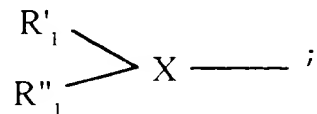
Please cancel claims 4, 5, 6, 24 and 26. Please amend claims 2, 3, 21, 22 so that they read as follows.

2. (twice amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is 1;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

R_1 is



X is N;

Inventors: Al-Obeidi et al.
Serial No.: 09/211,715 [9543]
Filed: December 14, 1998
Page 3

R'_1 is selected from the group consisting of isobutyl, 2-methylpentyl, cyclohexylmethyl, cyclohexenylmethyl, 2-methylbutyl, -H and 2,3-dimethylpentyl;

R''_1 is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzylimidazolyl, 2-naphthylmethyl, 5-pyridiminoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, 2-furoyl, 3,4-dichlorobenzoyl, 2-thienylacetyl, N(5-methyl-2-thienyl), ethoxycarbonyl, 2-fluorobenzoyl, t-butoxycarbonyl, benzyl and 1-20 amino acids;

R_2 is $-CR_{2A}R_{2B}-$, wherein $-R_{2A}$ and $-R_{2B}$ are independently selected from the group consisting of -H, 4-amidinophenylmethyl, 4-aminophenylmethyl, 2-naphthylmethyl, 4-(N-methylpyridinyl)methyl, (3-iodo-4-aminophenyl)methyl, (4-aminocarbonylphenyl)methyl, (3-iodo-4-hydroxyphenyl)methyl, (4-cyanophenyl)methyl, and (4-hydroxyphenyl)methyl;

R_3 is $-C(O)-$;

R_4 is $-NH-$;

Inventors: Al-Obeidi et al.
Serial No.: 09/211,715 [9543]
Filed: December 14, 1998
Page 4

R_5 is $-CR_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently selected from the group consisting of $-H$, 2-butyl, and cyclohexyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CR_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently selected from the group consisting of $-H$, 3-guanylpropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, and 4-(N-methylpyridinyl)methyl;

R_9 is $-C(O)-$; and

B is Leu-Pro-NH₂, Leu-Hyp-NH₂, Pen(CH₂COOH)-Pro-NH₂, Cys(CH₂COOH)-Pro-NH₂, γ -carboxyglutamic acid-Pro-NH₂, (N-carboxymethyl)Gly-Pro-NH₂, (N-carboxyethyl)Gly-Pro-NH₂, (N-1,3-dicarboxypropyl)Gly-Pro-NH₂, (N-methyl)Leu-Pro-NH₂, Leu-NH₂, Leu-OH, $-NH-(4\text{-trimethylammoniumbenzyl})$, $-NH-[4-(1\text{-methylpyridinium})methyl]$, and $-NH-(4\text{-amidinobenzyl})$.

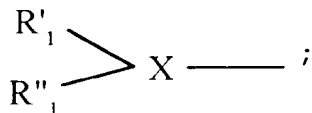
Inventors: Al-Obeidi et al.
Serial No.: 09/211,715 [9543]
Filed: December 14, 1998
Page 5

3. (twice amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is 1;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

R_1 is



X is N;

R'_1 is selected from the group consisting of H, isobutyl, 2-methylpentyl, cyclohexylmethyl, 3-quinolinyl, 2-methylbutyl, 2,3 dimethyl pentyl, and cyclohexenylmethyl;

R''_1 is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzimidazolyl, 2-naphthylmethyl, 5-pyrazinoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, and benzyl;

R_2 is $-CR_{2A}R_{2B}$, wherein $-R_{2A}$ and $-R_{2B}$ are independently selected from the group consisting of H, 3-amidinophenylmethyl, 4-amidinophenylmethyl,

Inventors: Al-Obeidi et al.
Serial No.: 09/211,715 [9543]
Filed: December 14, 1998
Page 6

4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-naphthylmethyl, 4-(N-methylpyridinyl)methyl, (3-iodo-4-aminophenyl)methyl, (4-aminocarbonylphenyl)methyl, (3-iodo-4-hydroxyphenyl)methyl, (4-cyanophenyl)methyl, and 3-indolylmethyl;

R_3 is selected from the group consisting of $-C(O)-$;

R_4 is $-NH-$;

R_5 is $-CR_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently selected from the group consisting of $-H$, 2-butyl, cyclohexyl and phenyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CR_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently selected from the group consisting of $-H$, 3-guanylpropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, N(carboxymethyl)(3-pyridinylmethyl), and 4-(N-methylpyridinyl)methyl;